Should clinical trial protocols be translated into the researchers' local language?

Ethics, science, and the language of research

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During 2006 eight hospitals in Spain participated in a multinational, multicenter randomized clinical trial sponsored by GSK[1] to test a vaccine for avian flu. The time to approval for the initial trial in Spain, which involved three hospitals in Madrid and two in Barcelona, was shortened substantially by skipping some steps in the approval process.[2] The Spanish drug regulatory agency (*Agencia Española de Medicamentos y Productos Sanitarios*, AEMPS) and participating centers' clinical trials ethics committees (*comités éticos de investigación clínica*) agreed to the abbreviated process because obtaining an avian flu vaccine was considered a high public health priority at the time.

One way in which the time to approval was shortened was by skipping translation into Spanish of the trial protocol. Only the protocol summary, the application to the AEMPS (the competent authority), and the informed consent form were translated into Spanish. The AEMPS agreed to issue its decision within 3 weeks from receipt of the application, and allowed the protocol to be submitted in English only as long as each participating center's clinical trials ethics committee agreed to consider the application based on the protocol in English rather than Spanish.

Although seemingly a departure from the spirit of Directive 2001/20/EC of the European Parliament and Council of 4 April 2001 (on the implementation of good clinical practice in the conduct of clinical trials on medical products for human use),[3] this abbreviated procedure appears to comply with current Spanish law regarding clinical trials,[4] since the law itself does not explicitly require translation of the protocol into Spanish.[5, 6] However, clinical trials ethics committees at hospitals in Spain often require translation of the protocol and investigator's brochure into Spanish; policies vary from center to center.

Postings during April 2007 to the MedTrad email listserve in response to news about the decision to dispense with translation of the protocol into the local language reflected a range of views from surprise and concern to acceptance that translation may not always be necessary. The main issue is how well researchers whose first language is not English can read and understand technical information in this language.[7] Translators, author's editors and medical writers who work with Spanish researchers have noted that the latter may overestimate their English reading comprehension skills and misunderstand texts as a result. In some settings language and communication experts and contract research organization (CRO) staff who liaise with researchers and translation providers are probably more familiar with researchers' actual language competencies than medical affairs managers, clinical trial managers or hospital ethics committee members.[8] Articles in this issue of *Panace@* examine the potential advantage and pitfalls of working with the protocol in English only.

What are the issues with translation?

Have unsatisfactory translations led clinical trial sponsors or CROs to conclude that translation is not worth the cost? Some MedTrad members familiar with clinical trial documentation and translation on both sides of the Atlantic have seen translation problems first hand: protocols in which the original meaning had been changed completely or was almost impossible to understand in some places because of translation errors. For example, one posting to the MedTrad list on 12 April 2007 mentioned a case in which the CRO opted to provide the researchers with the original English version of the protocol because they realized that the Spanish translation was not accurate enough to be useful. In this case the problematic translation had already been approved by the ethics committee and national competent authority, and therefore could not be corrected or changed in any way.

Have translation issues delayed the start or successful completion of clinical trials in the past? Dal-Ré and colleagues[2] do not say how much time they estimate was saved by skipping translation of the protocol into Spanish. However, in a presentation in 2006 on strategies to promote clinical research, Jaime Algorta of the Clinical Trials Unit of the Leia Foundation in Vitoria-Gasteiz, Spain,[9] reported that translation delayed the approval process by "about 15 days" and noted that in many cases, translation problems made it necessary to consult the original version. Yet it is not hard to find CROs, medical communication agencies and translation providers on the internet who specialize in clinical trial documents, and professional development organizations for translators are usually happy to help locate appropriate translators, often providing free, searchable access to lists of members and their areas of expertise.[10-12]

Some translation and medical communication agencies specialize in large translation assignments involving several languages for multinational clinical trials. An extreme case is reported on the internet by McElroy Translation.[13] This agency explains how they successfully translated material (some of it handwritten in the original English!) into nine languages (or eight, for those who consider Canadian and European French to be the same language) for an interim report of a very large clinical trial. Although this is probably an exceptional case, it shows that even very challenging transla-

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tion projects involving a huge volume of material and a short deadline can be completed successfully with good organization and management.

A study that surveyed CROs in several countries on their experiences with implementation of the European clinical trials directive noted that translation of the protocol into the local language is required in Spain.[14] This study, which included five CROs in Spain among its participants, concluded that most experiences with implementation of the European directive were good or very good. Of the 18 proposals handled by Spanish CROs, the national drug agency decision was delivered within or not more than 5 days past the 60-day deadline in 15 cases, and an average of 15 days past the deadline in only 3 cases. However, this study also noted that obtaining approval from hospital ethics committees in Spain could be very time-consuming, a complaint voiced in many pharmaceutical company analyses of the consequences of the European clinical trials directive. Gierend and colleagues[14] offer a sensible and implementable solution to administrative snafus and delays that managers of multinational clinical trials might encounter: "obtaining information about country-specific peculiarities before starting the submission."

This recommendation was echoed in a presentation titled "Global regulatory strategy" at the 43rd Annual Meeting of the Drug Information Association (DIA) in 2007, where Kay Mason, Senior Regulatory Affairs Manager at Quintiles Ltd., identified translation of the protocol or investigator's brochure into the local language as one of the many administrative steps that require lead time to be added to the calendar when planning a multinational clinical trial.[15]

Why the rush for approval for the avian flu vaccine trial?

The sponsor of the multinational, multicenter clinical trial referred to by Dal-Ré and colleagues[2] was their employer, GSK. Because of the media furor over the possibility of an avian flu pandemic, developing a bird flu vaccine was a high public health priority at the time. An additional factor that probably contributed to GSK's desire to accelerate the approval process was simultaneous research by a competitor, Sanofi-Pasteur, to develop a similar vaccine. The two multinational pharmaceutical companies were thus competitors in terms of both participant recruitment and earnings from a successful vaccine, if one were to be developed. Potential income from a product that nearly every individual in the world might want was probably a strong incentive to move ahead with the trial as swiftly as possible. However, the feared pandemic did not occur, and two years later – although virologists and epidemiologists continue to keep an eye on mutations of the bird flu virus – concerns over an imminent global public health emergency have subsided.

The language of research and ethics

Although presumably no effort is spared to obtain good translations of the patient information leaflet and informed consent form (because of the legal consequences of errors in these documents), many other documents are needed to run complex, costly multicenter clinical trials. A close analysis of the text of the clinical trials law in effect in Spain shows that – surprisingly – the current law retreats from earlier legislation in that translation into Spanish of the protocol is no longer mandatory.[5, 6, 16] Confusion regarding the requirement for translation probably arises from the fact that clinical trial regulations enacted by some autonomous regions in Spain go further than the national law and make translation of the protocol into the local language a legal requirement.

As several articles in this issue of *Panace@* point out, researchers are not the only readers of the protocol. Members of the clinical trials ethics committees of each participating center also need to examine this document closely in order to fulfill the committee's oversight mission. In Argentina, national law requires translation into Spanish in order to ensure that all members of the ethics committees (which, as in Spain, include lay persons and experts in disciplines other than medicine) are able to understand the protocol.[17] Their ability to provide a useful critique of the trial's potential methodological or ethical shortcomings would be compromised if some members of the ethics committee were unable to read English fluently.

If the documentation for running the trial is provided in English only, this may influence the number of researchers, administrators and ethics committee members and CRO staff in a non-English-speaking country who actually read the protocol carefully.[7] Could protocol violations or errors in data collection and recording occur because documents are not available in the researchers' first language? Is there a risk that some data from a trial might turn out to be useless if an investigator misunderstands the documents? Who would be responsible if any participants in the trial were inconvenienced or harmed because the documents were not available in the local language? Would the insurance policy the sponsor subscribes cover the cost of compensation to patients or other parties for damages caused by inadequate or missing translation and adaptation into the local language? These are questions that should concern clinical trial experts and clinical research regulators in any country where English is not the main language.

Conclusion: Change the law or change working methods?

Despite the administrative burden involved in complying with current European legislation affecting clinical trials, it should be remembered that Directive 2001/20/EC was developed to protect the best interests of all parties involved in clinical trial design, management and reporting: patients, industry and public sponsors, and regulatory agencies. Management problems are best solved by redesigning processes, not by complaining over the effort and expense compliance incurs, or by calling for changes in the law to make processes more convenient for drug companies. Experience has shown that it is possible to obtain national regulatory agency approval within the stipulated deadlines,[14] and that with forethought and foresight, it should be possible to organize translation of clinical trial documents in a timely manner that does not interfere with

ethical committee or competent authority approval, signing of the contract with the sponsor, or patient recruitment.[15, 18]

Clinical trial sponsors might put the quality of their processes at risk by cutting corners to reduce costs. A more useful alternative to management and language challenges is to work together with all stakeholders – competent authorities, ethics committees, CROs and other suppliers of research-related services to the pharmaceutical industry, including translators – to find ways to make processes more efficient. In this special issue of *Panace@* experts from several countries share their views on language, translation, and compliance with current clinical trial regulations. We hope their insights will help all parties involved in clinical trials to reach decisions regarding the language of research[19] that will protect patients from methodological or ethical oversights, and that will ensure the quality of the data that these complex, costly research instruments generate. Feedback and views from readers on language issues related with multinational clinical trials will be welcome, and should be submitted to the Editor, Bertha Gutiérrez Rodilla, at panacea@tremedica.org, María Luisa Clark at clarkcuba@comcast.net, or Karen Shashok at kshashok@kshashok.com.

References

1. Consejo General de Colegios Oficiales de Enfermería de España. Más de 1.500 voluntarios españoles prueban una vacuna contra gripe aviaria sin sufrir efectos adversos importantes. Available at <http://www.cge.enfermundi.com/servlet/Satellite?cid=1097662346229&id=1150377342588&pagename=SiteCGE/Noticia/TplNoticia_cge&categ=CatActualidad&idPG=1141051411357&p=1097662346229&dscateg=Actualidad&c=page>. Accessed 11 March 2008.
2. Dal-Ré R, García-Corbeira P, Morejón E. ¿Cuál es el tiempo mínimo necesario para iniciar un ensayo clínico multicéntrico en España? Medicina Clínica (Barc) 2007; 128 (7): 275.
3. 32001L0020. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal L 121 , 01/05/2001 P. 0034 - 0044. Available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0020:EN:HTML>. Accessed 14 April 2007.
4. Real Decreto 223/2004, de 6 de febrero. Available at <www.boe.es/boe/dias/2004/02/07/pdfs/A05429-05443.pdf>. Accessed 14 April 2007.
5. Villegas A. Análisis de los requisitos de idioma en la legislación española sobre ensayos clínicos. Panace@ 2008; IX (27): 64-66.
6. Gómez Polledo P. Traducir al español los protocolos de ensayos clínicos o no traducirlos: ¿qué dice la legislación española? Panace@ 2008; IX (27): 69-73.
7. Wager L. Should the entire clinical trial protocol always be translated into the local investigators' first language? Panace@ 2008; IX (27):75-76.
8. Fernández Piera M. Breve reflexión sobre la necesidad de las traducciones en los ensayos clínicos. ¿Qué precisan los lectores? Panace@ 2008; IX (27): 74.
9. Algorta J. Estrategias para la promoción de la investigación en el área de las nuevas tecnologías aplicadas a las ciencias de salud: Promoción de la investigación clínica. Presentation to the Seminario "Nanomedicinas y medicinas innovadoras". Universidad Internacional Menéndez Pelayo, Santander, August, 14-18, 2006. Available at <www.isciii.es/htdocs/presentacionyestructura/secretaria/pdf_uimp/X-J.Algorta-m.pdf>. Accessed 11 March 2008.
10. Asetrad: Asociación Española de Traductores, Correctores e Intérpretes. Buscar Profesionales. Available at <www.asetrad.org/index.asp?op=25>. Accessed 17 March 2008.
11. Chartered Institute of Linguists. Find-a-Linguist. Available at <http://www.iol.org.uk/linguist/translator1.asp>. Accessed 12 March 2008.
12. Translator Search. Institute of Translation & Interpreting. Directory of Members. Available at <www.iti.org.uk/indexMain.html>. Accessed 12 March 2008.
13. McElroy Translation. Clinical Trial–500,000 words into English in 27 days. Available at <www.mcelroytranslation.com/casestudies/antigenics/>. Accessed 20 February 2008.
14. Gierend M, Chase D, Feurer W. Experience with the implementation of the EU clinical trials directive–first results of a survey initiated by the BVMA e.V. Qual Assur J 2006; 10: 21-28.
15. Mason K. Global regulatory strategy. PowerPoint presentation at the 43rd Annual Meeting, Drug Information Association (DIA) Atlanta, GA, 2007. Available at <www.quintiles.com/NR/rdonlyres/E0FAEF89-68BB-4E3A-BB93-66F34969681C/0/KayMasonV2DIA2007.pdf>. Accessed 20 February 2008.
16. Clark ML. «A río revuelto…» o la traducción del protocolo de un ensayo clínico y sus meandros. Panace@ 2008; IX (27): 4-7.
17. Minsky GA. En la Argentina, traducir los protocolos al idioma local es un requisito jurídico y, sobre todo, ético. Panace@ 2008; IX (27): 67-68.
18. ACCOVION. European Door Opener. A modular solution to ease and plan European clinical trials. Available at <www.accovion.com/download/edo4122006.pdf>. Accessed 20 February 2008.
19. Brock-Utne B. Language of instruction and research in higher education in Europe: highlights from the current debate in Norway and Sweden. International Review of Education/Internationale Zeitschrift für Erziehungswissenschaft/Revue internationale l'éducation 2007; 53 (4): 367-388.